Supplementary Appendix

Supplemental Methods

Pharmacokinetic and Pharmacodynamic End Points
On day 1, pharmacokinetic samples for tocilizumab serum concentrations were drawn 0 to 4 hours before the start of the infusion and then within 15 minutes (to 1 hour) after the end of the infusion. Patients who received a second infusion of study drug provided an extra pharmacokinetic sample prior to and 15 minutes (to 1 hour) after the end of the infusion. If the second infusion fell within the window for the day 2 pharmacokinetic sample (20 to 24 hours postdose) for the first infusion, it could be combined with the postinfusion sample for the second infusion.

On day 1, interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), and CRP samples were drawn 0 to 4 hours before the start of the infusion and then within 15 minutes (to 1 hour) after the end of the infusion. Patents who received a second infusion of study drug provided extra samples for IL-6, sIL-6R, and CRP prior to and 15 minutes after the end of the infusion. If the second infusion fell within the window for the day 2 pharmacodynamic sample (20-24 hours) for the first infusion, it could be combined with the postinfusion sample for the second infusion.

Statistical Methods for Subgroup Analysis
The odds ratios for mortality at day 28 were compared between the tocilizumab treatment groups using logistic regression analysis for subgroups based on the following demographic and baseline disease characteristics: sex (male and female), age (18 to 65 years and >65 years), race (not White and White), and ordinal scale category at baseline (1 to 4 and 5 to 6).

Supplemental Results

Targeted Clinical Laboratory Results
No confirmed Hy law cases were reported, and no clinically relevant mean changes over time or differences between groups were observed for laboratory parameters.

SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction Test Results
At baseline, 43 of 46 patients (93.5%) in each treatment group had a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) result based on a nasopharyngeal or bronchoalveolar lavage (BAL) sample performed at a central testing laboratory; 3 in each group had a negative result, and 5 were not tested at the central laboratory or had missing values. The median (range) RT-PCR SARS-CoV-2 viral load in nasopharyngeal swab or BAL samples at baseline, including those with a negative result (imputed to 0.06 copies/µL) and those with a positive result below the limit of quantification (imputed to 0.12 copies/µL) was 30.56 (range, 0.1-14,458.9) copies/µL in the 4-mg/kg group and 8.51 (range, 0.1-132,429.0) copies/µL in the 8-mg/kg group; levels declined throughout the study in both treatment groups. No clear differences were observed between the 2 groups in the time to RT-PCR SARS-CoV-2 negativity; 20 patients (41.7%) in the 4-mg/kg group and 22 (45.8%) in the 8-mg/kg group had a negative RT-PCR SARS-CoV-2 result by day 28. In the cause-specific analysis, in which death was considered a competing event, the hazard ratio for RT-PCR negativity was 0.978 (95% CI, 0.51 to 1.87; reference 8-mg/kg group).

Supplemental Table 1. Seven-Category Ordinal Scale

Category	Clinical status
1	Discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen)
2	Non-ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen
3	Non-ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen
4	ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen
5	ICU, requiring intubation and mechanical ventilation
6	ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support (eg, vasopressors or renal replacement therapy)
7	Death

This ordinal scale has equivalent categories as those in the World Health Organization ordinal scale for COVID-19[1] and was discussed and agreed upon with health authorities.

ICU, intensive care unit.

1. World Health Organization. WHO R&D blueprint novel coronavirus COVID-19 therapeutic trial synopsis. Accessed October 23, 2020. https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

Supplemental Table 2. Study Drug Exposure in the Safety Population

	Tocilizumab 4 mg/kg (n=49)	**Tocilizumab 8 mg/kg (n=48)**
Doses administered, n (%)		
1	37 (75.5)	39 (81.3)
2	12 (24.5)	9 (18.8)
Time from first dose to second dose, h		
n	12	9
Mean (SD)	17.8 (4.6)	19.4 (3.3)
Median (range)	18.8 (10.4-22.6)	19.8 (13.2-23.1)
Total cumulative dose, mg		
Mean (SD)	442.4 (203.2)	812.4 (301.0)
Median (range)	380.1 (179.8-1034.6)	739.8 (500.1-1601.1)
Patients with a reason for second tocilizumab infusion, n/N (%)	12 (24.5)	9 (18.8)
Sustained fever	1/49 (2.0)	1/48 (2.1)
Supplemental oxygen requirement increase	9/49 (18.4)	4/48 (8.3)
Other	2/49 (4.1)	4/48 (8.3)

Supplemental Table 3. Summary of Previous Antiviral Treatments[a] in the Safety Population

n (%)	Tocilizumab 4 mg/kg (n=49)	Tocilizumab 8 mg/kg (n=48)
Patients with ≥1 treatment	13 (26.5)	13 (27.1)
Total treatments	14	16
Remdesivir	12 (24.5)	11 (22.9)
Hydroxychloroquine	2 (4.1)	3 (6.3)

[a] Included antiviral treatments (lopinavir-ritonavir, remdesivir, lopinavir, ritonavir, chloroquine, hydroxychloroquine, and hydroxychloroquine sulfate) taken within 7 days of baseline and ending before the first dose of tocilizumab.

Supplemental Table 4. Summary of Pharmacokinetic Parameters in the Pharmacokinetic Population (Evaluable Profiles)

	Tocilizumab 4 mg/kg		**Tocilizumab 8 mg/kg**	
	1 Dose (n=35)	**2 Doses (n=12)**	**1 Dose (n=38)**	**2 Doses (n=9)**
AUC_{0-28}, µg/mL·day				
Mean (SD)	382 (143)	903 (293)	885 (251)	1430 (268)
Median (range)	371 (196-1040)	837 (592-1480)	849 (471-1500)	1330 (1130-1810)
Geometric mean (CV)	363 (0.310)	864 (0.309)	851 (0.286)	1410 (0.184)
C_{max}, µg/mL				
Mean (SD)	83 (19)	159 (31)	156 (32)	253 (51)
Median (range)	82 (49-134)	150 (110-203)	159 (101-234)	228 (198-363)
Geometric mean (CV)	80 (0.233)	156 (0.200)	153 (0.208)	249 (0.188)
CL, L/day				
Mean (SD)	0.459 (0.107)	0.489 (0.11)	0.530 (0.199)	0.653 (0.206)
Median (range)	0.451 (0.261-0.697)	0.468 (0.327-0.701)	0.487 (0.179-1.160)	0.629 (0.376-1.020)
Geometric mean (CV)	0.447 (0.238)	0.477 (0.224)	0.496 (0.369)	0.624 (0.320)
V_c, L				
Mean (SD)	4.31 (1.0)	4.13 (0.80)	4.57 (1.13)	4.91 (1.23)
Median (range)	4.14 (2.47-7.11)	4.20 (2.54-5.17)	4.34 (3.08-7.88)	4.57 (3.59-7.27)
Geometric mean (CV)	4.20 (0.232)	4.05 (0.211)	4.45 (0.236)	4.79 (0.235)

AUC_{0-28}, area under the curve to day 28; CL, linear clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; V_c, volume of the central compartment.

Supplemental Table 5. Deaths to Days 14, 28, and 60 and Summary of Causes of Death[a] to Day 60 in the Safety Population

n (%)	Tocilizumab 4 mg/kg (n=49)	Tocilizumab 8 mg/kg (n=48)	All patients (N=97)
Total number of deaths			
To day 14	4 (8.2)	3 (6.3)	7 (7.2)
To day 28	7 (14.3)	5 (10.4)	12 (12.4)
To day 60	8 (16.3)	6 (12.5)	14 (14.4)
Infections			
COVID-19 pneumonia	3 (6.1)	1 (2.1)	4 (4.1)
Pneumonia	0	1 (2.1)	1 (1.0)
Sepsis	1 (2.0)	0	1 (1.0)
Metabolism and nutrition disorders			
Failure to thrive	2 (4.1)	0	2 (2.1)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	0	2 (4.2)	2 (2.1)
Acute respiratory distress syndrome	0	1 (2.1)	1 (1.0)
Aspiration	1 (2.0)	0	1 (1.0)
Dyspnea	1 (2.0)	0	1 (1.0)
General disorders and administration site conditions			
Multiple organ dysfunction syndrome	0	1 (2.1)	1 (1.0)

[a] Investigator text for adverse events were encoded using the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.0. For frequency counts by preferred term, multiple occurrences of the same adverse event in an individual were counted only once.

Supplemental Table 6. Adverse Events of Special Interest[a] to Day 60 in the Safety Population

n (%)	Tocilizumab 4 mg/kg (n=49)	Tocilizumab 8 mg/kg (n=48)
Infections[b]	8 (16.3)	5 (10.4)
Bleeding events	4 (8.2)	2 (4.2)
Hypersensitivity reactions	0	2 (4.2)
Anaphylactic reaction events	0	1 (2.1)
Anaphylactic reaction events (Sampson)	0	1 (2.1)
Hepatic events	0	1 (2.1)
Stroke	0	1 (2.1)
Demyelinating events	0	0
Gastrointestinal perforations	0	0
Malignancies	0	0
Myocardial infarction	0	0
Opportunistic infections	0	0

[a] Investigator text for adverse events were encoded using the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.0. For frequency counts by preferred term, multiple occurrences of the same adverse event in an individual were counted only once.
[b] No fungal infections were observed.

Supplemental Table 7. Summary of Exploratory Efficacy Endpoints in Modified Intention-to-Treat Population

	Tocilizumab 4 mg/kg (n=49)	**Tocilizumab 8 mg/kg (n=48)**	**Median of pairwise differences (95% CI)**	**Hazard ratio (95% CI)**	**Weighted difference (95% CI)**
Clinical status based on 7-category ordinal scale, median (95% CI)					
Day 14	1.00 (1.00 to 3.50)	1.00 (1.00 to 3.00)	0.00 (0.00 to 0.00)	NA	NA
Day 28	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	0.00 (0.00 to 0.00)	NA	NA
Time to hospital discharge or "ready for discharge"[a] by day 28, n (%)	39 (79.6)	38 (79.2)	NA	0.876 (0.55 to 1.40)	NA
Mortality rate at day 28, n (%) [95% CI]	7 (14.3) [4.5 to 24.1]	5 (10.4) [1.8 to 19.1]	NA	NA	−4.5 (−18.2 to 9.2)
Incidence of mechanical ventilation[b] at day 28, n (%) [95% CI]	14 (28.6) [15.9 to 41.2]	15 (31.3) [18.1 to 44.4]	NA	NA	1.5% (−16.4 to 19.5)

Incidence of initiation of mechanical ventilation[c] at day 28, n (%) [95% CI]	10 (22.2) [10.1 to 34.4]	8 (19.5) [7.4 to 31.6]	NA	NA	−3.2% (−20.6 to 14.1)

[a] "Ready for discharge" was defined as normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen as assessed by hospital records.

[b] Included patients who were receiving mechanical ventilation at baseline.

[c] Among patients not receiving mechanical ventilation at baseline.

Supplemental Figure Legends

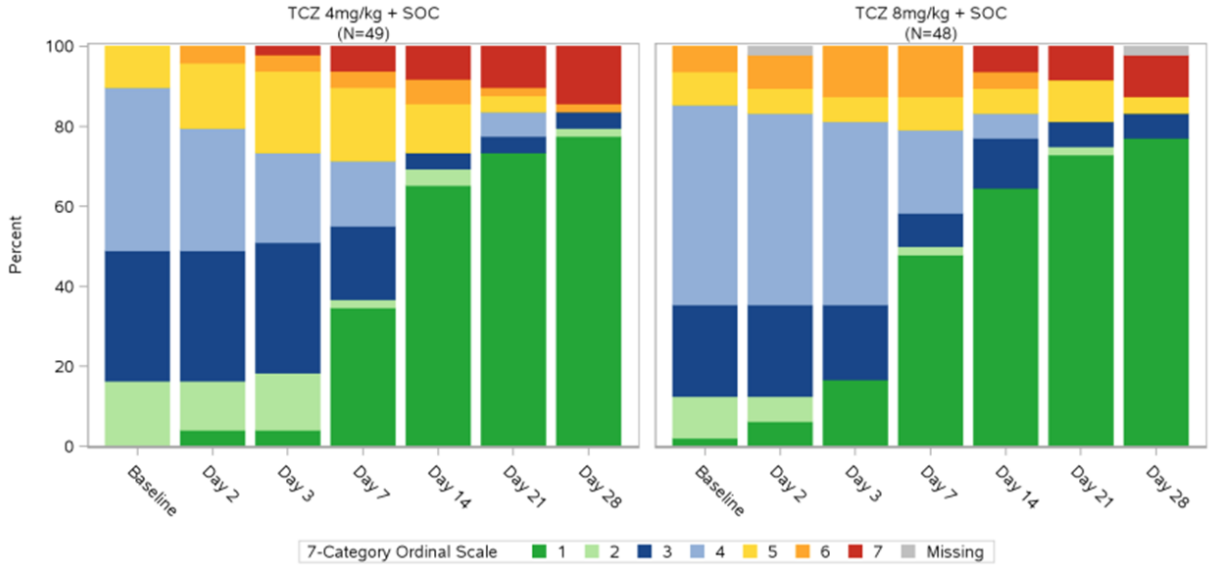
Supplemental Figure 1. Clinical Status Using Seven-Category Ordinal Scale[a] Over Time to Day 28. Data presented without imputation, except in cases of patients without data for days following a score of 7 that was imputed as such. Patients without data for days following a score of 1 were imputed as such until a score other than 1 was recorded. Abbreviations: ICU, intensive care unit; SOC, standard of care; TCZ, tocilizumab.[a] Seven-category ordinal scale: 1, discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen); 2, non-ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen; 3, non-ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen; 4, ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Supplemental Figure 2. Time to Hospital Discharge[a]: Cumulative Distribution Plot to Day 28 in Modified Intention-to-Treat Population.[b] SOC, standard of care; TCZ, tocilizumab.
[a] "Ready for discharge" was defined as normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen. [b] Patients who discontinued were censored at their last ordinal scale assessment before discontinuation. Patients who died were censored at day 28.

Supplemental Figure 3. Forest Plot of Logistic Regression Analysis of Mortality by Subgroup in Modified Intention-to-Treat Population. Odds ratios within each subgroup were calculated by logistic regression analysis for mortality. Each logistic regression model included the treatment

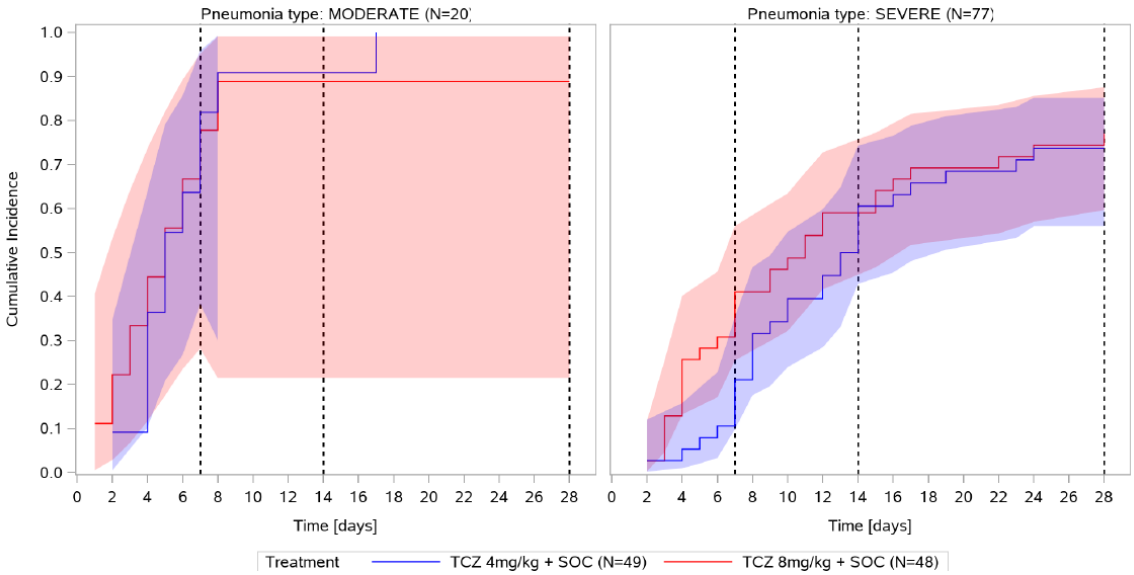
term and baseline subgroup term (as defined in the table). An odds ratio of <1 indicated more events in the 8-mg/kg group than the 4-mg/kg group. Race category of “not White” was defined as “multiple,” “native Hawaiian or other Pacific Islander,” “American Indian or Alaska native,” “Asian,” “Black or African American,” and “unknown.” 95% CIs were calculated using the Wald method. Abbreviations: SOC, standard of care; TCZ, tocilizumab.

Supplemental Figure 1. Clinical Status Using Seven-Category Ordinal Scale[a] Over Time to Day 28



Data presented without imputation, except in cases of patients without data for days following a score of 7 that was imputed as such. Patients without data for days following a score of 1 were imputed as such until a score other than 1 was recorded.
ICU, intensive care unit; SOC, standard of care; TCZ, tocilizumab.
[a] Seven-category ordinal scale: 1, discharged (or ready for discharge as evidenced by normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen); 2, non-ICU hospital ward (or ready for hospital ward), not requiring supplemental oxygen; 3, non-ICU hospital ward (or ready for hospital ward), requiring supplemental oxygen; 4, ICU or non-ICU hospital ward, requiring noninvasive ventilation or high-flow oxygen; 5, ICU, requiring intubation and mechanical ventilation; 6, ICU, requiring extracorporeal membrane oxygenation or mechanical ventilation and additional organ support; 7, death.

Supplemental Figure 2. Time to Hospital Discharge[a]: Cumulative Distribution Plot to Day 28 in Modified Intention-to-Treat Population[b]

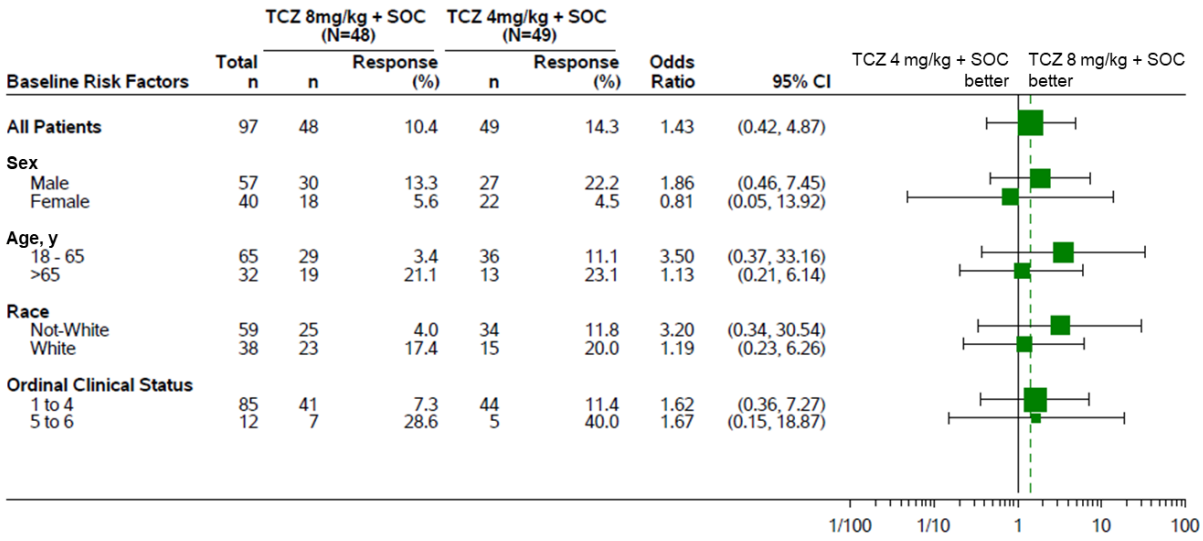


SOC, standard of care; TCZ, tocilizumab.

[a] "Ready for discharge" was defined as normal body temperature and respiratory rate and stable oxygen saturation on ambient air or ≤2 L of supplemental oxygen.

[b] Patients who discontinued were censored at their last ordinal scale assessment before discontinuation. Patients who died were censored at day 28.

Supplemental Figure 3. Forest Plot of Logistic Regression Analysis of Mortality by Subgroup in Modified Intention-to-Treat Population



Odds ratios within each subgroup were calculated by logistic regression analysis for mortality. Each logistic regression model included the treatment term and baseline subgroup term (as defined in the table). An odds ratio of <1 indicated more events in the 8-mg/kg group than the 4-mg/kg group. Race category of “not White” was defined as “multiple,” “native Hawaiian or other Pacific Islander,” “American Indian or Alaska native,” “Asian,” “Black or African American,” and “unknown.” 95% CIs were calculated using the Wald method.

SOC, standard of care; TCZ, tocilizumab.